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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/517,544	HAYASHIZAKI ET AL.	
	Examiner	Art Unit	
	Angela M. Bertagna	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 August 2009 and 27 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9,10,12-17,19-25,34-51,57 and 58* is/are pending in the application.

4a) Of the above claim(s) *34-51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,10,12-17,19-25,57 and 58* is/are rejected.

7)☒ Claim(s) *17* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/30/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submissions filed on August 13, 2009 and on November 27, 2009 have been entered.

Claims 9, 10, 12-17, 19-25, 34-51, 57, and 58 are currently pending. In the response, Applicant amended claims 9, 10, 12, 17, 20, 23, and 24. Claims 34-51 remain withdrawn from consideration as being drawn to a non-elected invention.

Information Disclosure Statement

2. Applicant's submission of an Information Disclosure Statement on July 30, 2009 is acknowledged. A signed copy is enclosed.

Specification

3. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: The specification does not appear to provide proper antecedent basis for the use of silicagel matrix as recited in claims 16 and 58 or for the use of the enzymes BpmI and BsgI as recited in claim 25.

Claim Objections

4. Claim 17 is objected to because of the following informalities: This claim appears to contain a typographical error. It would appear that "synthesized in step (ii)" or "obtained in step (iii)" was intended for "synthesized in step (iii)", which appears in step (iv).

Appropriate correction is required.

Claim Rejections - 35 USC § 112, 2nd paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 24 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 24 is indefinite, because the scope of the claim is unclear. Claim 24 recites that the restriction enzyme is "selected from the group comprising the Class IIG and Class IIS restriction enzymes". The recitation "selected from the group comprising" before a Markush group is improper Markush language (see MPEP 2173.05(h)), because it implies that the Markush group may include members other than the recited Class IIG and Class IIS restriction enzymes. Since the identity of these other restriction enzymes encompassed by the claim is not clear, the scope of claim 24 is indefinite. Amendment of the claim to recite "selected from the group consisting of the Class IIG and Class IIS restriction enzymes" or "wherein the restriction enzyme is a Class IIG or Class IIS restriction enzyme" would likely overcome the rejection.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 17, 19-21, and 23-25 are rejected under 35 U.S.C. 102(e) as being anticipated by Pedersen (US 2003/0113737 A1; cited previously).

These claims are drawn to a method for preparing a double-stranded DNA fragment corresponding to the 5' end of an mRNA comprising linker ligation and restriction enzyme digestion.

Regarding claim 17, Pedersen teaches a method for preparing a double-stranded DNA fragment comprising a nucleotide sequence corresponding to the most 5' end of an mRNA that comprises:

(a) preparing a nucleic acid that corresponds to a nucleotide sequence of the 5' end of an mRNA (see Figure 12, steps I & II and paragraphs 61, 254 and 261-262, where the decapped mRNA is prepared)

(b) attaching at least one linker to the nucleic acid by:

(i) attaching a linker to an end region corresponding to the most 5' end of the mRNA, wherein the linker contains a recognition sequence for a restriction enzyme that cleaves at a site different from its recognition sequence (see Figure 12, step III and paragraphs 61, 254 and 261-262, where the adapter, which has recognition sequences (A)

and (B) for a nicking endonuclease and a Type IIS restriction enzyme, respectively, is ligated to the 5' end of the decapped mRNA)

(ii) synthesizing a first strand cDNA using the mRNA having the linker attached as a template (see Figure 12, step IV and paragraphs 61, 254 and 261-262, where reverse transcription using random decamers is taught)

(iii) removing the mRNA (see Figure 12, step V and paragraphs 61, 254 and 261-262, where the second strand synthesis step inherently removes the mRNA by strand displacement)

(iv) synthesizing a second strand cDNA using the first strand cDNA as a template (see Figure 12, step V and paragraphs 61, 254 and 261-262)

(c) cleaving the nucleic acid with the Type IIS restriction enzyme and the nicking enzyme (paragraph 263)

(d) collecting the resulting fragment corresponding to the most 5' end of the mRNA (see Figure 14 and paragraph 63, and paragraphs 262-264; see also Figure 12 and paragraph 61, which teach that the cleavage with the nicking enzyme and the Type IIS restriction enzyme as described in paragraph 263 generates a fragment corresponding to the 5' terminus of the mRNA).

Regarding claim 19, Pedersen teaches that the second strand cDNA is synthesized using a primer that has the sequence of the linker (paragraphs 61 and 261). These primers are inherently partially complementary to the linker region (*i.e.* they contain at least 2 consecutive nucleotides that are complementary to the linker region - see pages 30-33 for specific examples of such adapters).

Regarding claims 20 and 21, Pedersen teaches that a selective binding substance, specifically biotin, is attached to the oligonucleotide primers used to synthesize second strand cDNA and that the products of the second strand synthesis reaction are recovered using a solid support having streptavidin immobilized thereupon (see paragraphs 262-264).

Regarding claims 23-25, Pedersen teaches that the restriction enzyme is a Class IIS restriction enzyme (see paragraphs 61, 254, and 262-263), such as Bpm I (paragraphs 785 & 791) or BsgI (page 31).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pedersen (US 2003/0113737 A1; cited previously) in view of Cocuzza et al. (US 5,484,701; cited previously).

Pedersen teaches the method of claims 17, 19-21, and 23-25, as discussed above.

Pedersen teaches that the oligonucoleotide primer used in the second strand cDNA synthesis step contains biotin to permit streptavidin-mediated capture rather than digoxigenin to permit capture with an anti-digoxigenin antibody (see above).

Cocuzza teaches a method for isolating primer extension products prior to electrophoresis comprising biotinylation of the primer extension product and isolation with a support-immobilized avidin (abstract and column 3, line 55 – column 4, line 20). Regarding claim 22, Cocuzza teaches that biotinylated primer extension products may also be isolated using an antibody-antigen capture system, wherein the antigen digoxigenin is attached to the primer and the primer extension products are captured with a support-immobilized anti-digoxigenin antibody (column 7, lines 28-43). In this passage, Cocuzza further teaches that this system performs as well as the biotin-avidin system, and that methods for immobilizing antibodies on solid supports are known.

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to substitute the biotin-streptavidin capture method taught by Pedersen with the digoxigenin-anti-digoxigenin antibody capture method taught by Cocuzza. An ordinary artisan would have been motivated to do so with a reasonable expectation of success, since Cocuzza taught that digoxigenin-mediated capture was an art-recognized equivalent of the biotin-avidin capture method taught by Pedersen (column 7, lines 28-43). As noted in MPEP 2144.06, substitution of art-recognized equivalents known to be useful for the same purpose is *prima facie*

obvious in the absence of unexpected results. In this case, no evidence of unexpected results with respect to the use of digoxigenin has been presented. Accordingly, the method of claim 22 is *prima facie* obvious over Pedersen in view of Coccuza.

10. Claims 9, 10, 12, 14, 16, and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shibata et al. (BioTechniques (2001) 30: 1250-1254; cited previously) as evidenced by Carninci et al. (Genomics (1996) 37: 327-336; cited previously) in view of Kaufman et al. (US 6,383,754 B1; cited previously).

These claims are drawn to a method for preparing a DNA fragment corresponding to the 5' end of an mRNA that comprises affinity purification based on the cap structure at the 5' end of mRNA, linker ligation, and digestion with a Type IIS restriction enzyme.

Shibata teaches a method for preparing a DNA fragment corresponding to the most 5' end of an mRNA (see abstract and Figure 1).

Regarding claims 9, 10, 12, 14, 16, and 58, Shibata teaches preparing a nucleic acid corresponding to the most 5' end of an mRNA by performing the "cap trapper" method, which comprises producing and isolating a first strand cDNA molecule corresponding to the most 5' end of an mRNA of interest, ligating a double-stranded linker having a recognition and cleavage site for a restriction enzyme within the linker to the end of the cDNA that corresponds to the most 5' end of the mRNA molecule, synthesizing second-strand cDNA using the linker as a primer to produce a ligation product comprising the linker and a full-length double-stranded cDNA molecule, cleaving the resulting ligation product with the restriction enzyme, and collecting a DNA fragment corresponding to the 5' most end of the mRNA (see pages 1250-1252

and Figure 1). As evidenced by the Carninci reference (see Figure 1 and pages 328-331), which was cited by Shibata as providing the specific details of the cap trapper method, the cap trapper step of the method of Shibata comprises synthesizing first-strand cDNA using mRNA as a template to produce cDNA/mRNA hybrids, capturing cDNA/mRNA hybrids having a biotinylated 5' cap structure on the mRNA portion of the hybrids using streptavidin-coated magnetic beads, and recovering the cDNA portion of the hybrids.

The method of Shibata utilizes a restriction enzyme that cleaves at its recognition site in the linker (see Figure 1) rather than an enzyme that cleaves at distance separated from its recognition site (*e.g.,* a Type IIS restriction enzyme) as required by independent claims 9 and 12.

Kaufman teaches a method for analyzing a plurality of nucleic acids via the generation of sequence-encoded tags (see abstract and column 4, lines 19-47). The method of Kaufman comprises: (i) digesting a nucleic acid population to generate a plurality of fragments, ligating a double-stranded linker (*i.e.,* an offset adapter) that has a recognition site for a Type IIS restriction within the linker to the same end of each of the fragments, digesting the resulting ligation products with a Type IIS restriction enzyme to produce a plurality of fragments comprising the linker and a short nucleotide sequence tag, and analyzing the resulting tags via mass spectroscopy or microarray analysis (see, for example, column 4, lines 19-47 and Illustrations 1 and 2 at columns 42-48). Kaufman teaches that the inclusion of a Type IIS recognition sequence in the offset adapters is useful, because Type IIS restriction enzymes function as a "universal restriction enzyme", cleaving a nucleic acid a predetermined number of bases away from the recognition site to produce a plurality of fragments having different termini but a defined length (column 9, line 64 – column 10, line 13 and column 23, line 24-44). Kaufman also teaches that

the sets of sequence tags produced using the disclosed methods produce characteristic sets of tags from complex nucleic acid samples, and therefore provide a means for the rapid, reproducible, and sequence-specific cataloging of complex nucleic acid samples (column 4, lines 48-63).

It would have been *prima facie* obvious to apply the teachings of Kaufman to the methods disclosed by Shibata. Specifically, an ordinary artisan would have been motivated to include a recognition site for a Type IIS restriction enzyme in the linker used in the method of Shibata in order to obtain the ability to generate libraries of sequence tags, which Kaufman taught were a useful complement to conventional cDNA libraries, such as those obtained via the method of Shibata, as they provide a means for the rapid, reproducible, and sequence-specific cataloging of complex nucleic acid samples (see above). An ordinary artisan also would have been motivated to include a Type IIS restriction enzyme recognition site in the linker used in the methods of Shibata in order to gain the advantages described by Kaufman with respect to these "universal restriction enzymes" (see column 9, line 64 - column 10, line 5). Thus, the methods of claims 9, 10, 12, 14, 16, and 58 are *prima facie* obvious over Shibata as evidenced by Carninci in view of Kaufman.

11. Claims 13 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shibata et al. (BioTechniques (2001) 30: 1250-1254; cited previously) as evidenced by Carninci et al. (Genomics (1996) 37: 327-336; cited previously) in view of Kaufman et al. (US 6,383,754 B1; cited previously) and further in view of Edery et al. (Molecular and Cellular Biology (1995)

15(6): 3363-3371; cited previously) and further in view of Das et al. (Physiological Genomics (2001) 6: 57-80; cited previously).

The combined teachings of Shibata as evidenced by Carninci and Kaufman render obvious the methods of claims 9, 10, 12, 14, 16, and 58 as discussed above.

These references do not teach using a cap-binding protein or a cap-binding antibody attached to a solid support to selectively capture mRNA/cDNA hybrids in which the mRNA component of the hybrid possesses the 5' cap structure as required by claims 13 and 57.

Edery teaches a method ("CAPture") for isolating full-length cDNA transcripts or cDNA transcripts having the most 5' end that comprises affinity capture using the cap-binding protein eIF-4e (see abstract). The method of Edery comprises the following steps: reverse transcribing mRNA to generate cDNA/mRNA hybrids, treating the reverse transcription reaction with RNase A treatment to remove contaminating single-stranded RNA, binding eIF-4e to the 5' cap structure of the mRNA component of the hybrids to selectively bind full-length mRNA/cDNA hybrids, and capturing the bound eIF-4e/mRNA/cDNA complexes using an anti-eIF-4e antibody conjugated to sepharose beads (see page 3364, column 2 – page 3365, column 1 and Figure 4).

Das reviewed methods for obtaining full-length cDNA molecules. Das compared the affinity selection methods taught by Carninci (*i.e.,* "cap trapper") and Edery (*i.e.,* affinity selection using the cap-binding protein eIF-4e) and reported that the cap trapper method of Carninci method was not specific. Specifically, Das stated:

> [I]f we compare the ability of cap trapper to discriminate between cDNA duplex with capped mRNA (generated *in vitro*) or duplexed with uncapped mRNA (generated *in vitro*), then we are unable to obtain specific selection of capped over uncapped transcripts (J. Pelletier, data not shown). This is likely due to the fact that biotin-hydrazide can also react with unoxidized RNA due to incipient reaction of cytosine residues. Hence, addition of biotin is not solely directed toward the

> cap structure. Also, it is important to note that the oxidation reaction with $NaIO_4$ is difficult to control, and the molar ratio of periodate to substrate is important, otherwise one gets destruction of base rings (page 73).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to substitute the affinity selection method of Edery based on eIF-4e for the cap trapper method taught by Carninci when practicing the method resulting from the combined teachings of Shibata and Kaufman. An ordinary artisan would have been motivated to do so with a reasonable expectation of success, since Das taught that the affinity selection method based on eIF-4e-mediated capture was more specific than the cap trapper method and advantageously avoided the use of the potentially RNA-degrading reagent $NaIO_4$ (see above). Thus, the methods of claims 13 and 57 are *prima facie* obvious in view of the combined teachings of the cited references.

12. Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Shibata et al. (BioTechniques (2001) 30: 1250-1254; cited previously) as evidenced by Carninci et al. (Genomics (1996) 37: 327-336; cited previously) in view of Kaufman et al. (US 6,383,754 B1; cited previously) and further in view of Merenkova et al. (US 6,022,715; cited on an IDS and newly applied).

The combined teachings of Shibata as evidenced by Carninci and Kaufman render obvious the methods of claims 9, 10, 12, 14, 16, and 58 as discussed above.

These references teach that the 5' cap structure of the mRNA is biotinylated to permit selective capture with streptavidin-coated magnetic beads, whereas claim 15 requires the 5' cap structure to be modified with digoxigenin to permit capture with an anti-digoxigenin antibody.

Merenkova teaches a method for isolating full-length cDNA molecules. The method of Merenkova comprises modifying the 5' cap structure of an mRNA to contain a molecule, such as biotin or digoxigenin, that may be selectively captured by its binding partner (*i.e.,* streptavidin or an anti-digoxigenin antibody, respectively) immobilized on a solid support, synthesizing first-strand cDNA using the modified mRNA molecules as a template to produce cDNA/mRNA hybrids, selectively capturing hybrids based on the modification present on the 5' cap, and digesting the mRNA component of the captured hybrids, thereby obtaining a full-length cDNA corresponding to the complete mRNA (see abstract, column 5, line 55 – column 6, line 38, and column 6, line 60 – column 7, line 12).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to substitute the biotin-streptavidin capture method taught by Shibata with the digoxigenin-anti-digoxigenin antibody capture method taught by Merenkova. As noted above, Merenkova expressly taught that biotin and digoxigenin were equivalent means for labeling the 5' cap structure of an mRNA molecule to permit subsequent capture using a support-immobilized binding partner (*i.e.,* streptavidin or an anti-digoxigenin antibody). Therefore, an ordinary artisan would have been motivated to substitute one equivalent for the other with a reasonable expectation of success. See also MPEP 2144.06, which states that the substitution of art-recognized equivalents known to be useful for the same purpose is *prima facie* obvious in the absence of unexpected results. In this case, no evidence of secondary considerations with respect to the use of digoxigenin has been presented, and therefore, the method of claim 15 is *prima facie* obvious in view of the combined teachings of the cited references.

Response to Arguments

13. Applicant's arguments filed on August 13, 2009 have been fully considered, and they were persuasive, in part.

Claim Objections

Regarding the objections to claims 10, 12, 17, 23, and 24, Applicant argues that the amendments have obviated the objections (see page 9). This argument was persuasive with respect to claims 10, 12, 23, and 24, and therefore, the objections to these claims have been withdrawn. Applicant's arguments were not persuasive with respect to claim 17, however. As discussed above, this claim still appears to contain a typographical error, and therefore, the objection to claim 17 has been maintained.

Rejection under 35 U.S.C. 112, second paragraph

Applicant's arguments, see pages 9-10, filed on August 13, 2009, regarding the rejection of claims 9, 10, 12-17, 19-25, 57, and 58, under 35 U.S.C. 112, second paragraph have been fully considered and are persuasive. As noted by Applicant at page 10, the claim amendments have obviated the antecedent basis issues raised in the rejection. Also, as discussed by Applicant at pages 9-10, the relationship between the mRNA and RNA molecules manipulated during the claimed processes would be clear to the ordinary artisan. Accordingly, the rejection has been withdrawn.

Rejection under 35 U.S.C. 102(e) citing Pedersen

Regarding the rejection of claims 17, 19-21, and 23-25 under 35 U.S.C. 102(e) as being anticipated by Pedersen, Applicant argues that the methods disclosed in Pedersen only produce single-stranded DNA molecules, since the digestion step is conducted with a nicking endonuclease and a Type IIS restriction endonuclease (pages 11-12). Applicant argues, therefore, that the reference does not teach production of a double-stranded DNA fragment corresponding to the most 5' end of an mRNA molecule as required by the claims and further points to paragraphs 791-793 of the reference to support this argument (page 12).

Applicant's arguments regarding the teachings of Pedersen have been fully considered, but they were not persuasive. Although digestion with the nicking endonuclease and Type IIS restriction endonuclease as described by Pedersen produces a single-stranded nucleic acid tag rather than a double-stranded nucleic acid tag (see Figure 12 and the accompanying description at paragraphs 61, 261, and 262, for example), the single-stranded tag is subsequently captured (*i.e.,* collected) via hybridization and ligation to a double-stranded adapter (see Figure 13 and paragraphs 262-264, as discussed above). This results in "collecting a resulting double-stranded DNA fragment corresponding to the most 5' end of the mRNA" as required by claim 17. It is noted that the claims are written in open, "comprising" language, and as a result, they do not exclude performing an additional step or steps after the Type IIS digestion step to obtain and collect a double-stranded DNA fragment corresponding to the 5' most end of the RNA. Since Applicant's arguments were not persuasive, the rejection has been maintained with modifications.

Rejection under 35 U.S.C. 103(a) citing Pedersen and Cocuzza

Regarding the rejection of claim 22 under 35 U.S.C. 103(a) as being unpatentable over Pedersen in view of Cocuzza, Applicant first argues that the combined teachings of the cited references do not teach ligating the first strand cDNA to a double-stranded linker that is subsequently used to prime second-strand cDNA synthesis (pages 13-14).

This argument was not persuasive, because the rejected claims do not currently require this step. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). It is also noted that the portion of the Office Action mailed on March 4, 2008 referred to by Applicant in the response was directed to claim 18, which has been canceled. As discussed previously, the limitations of claim 18 (*i.e.,* ligating a first strand cDNA to a double-stranded linker that is subsequently used to prime second-strand cDNA synthesis) have not been incorporated into any of the currently pending claims. The currently pending claims only require synthesizing a second strand cDNA using the first-strand DNA as a template and oligonucleotides partially or completely complementary to the linker attached to the mRNA, which, as discussed above, is taught by Pedersen. Therefore, the fact that neither Pedersen nor Cocuzza teach ligating a first strand cDNA to a double-stranded linker that is subsequently used to prime second-strand cDNA synthesis is irrelevant to the currently pending claims.

Applicant also argues that the Cocuzza reference is non-analogous art (see page 13). In response to this argument, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed

invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In the instant case, the teachings of Cocuzza regarding the use of digoxigenin-mediated purification of nucleic acids compared to biotin-avidin purification systems would have been reasonably pertinent to the problem with which Applicant and Pedersen was concerned, namely the use of a specific binding pair (*e.g.* biotin-avidin or digoxigenin) for selective, affinity-based nucleic acid purification. Therefore, the Cocuzza reference is not considered to be non-analogous art.

Applicant also argues that there is no motivation to combine the teachings of Cocuzza and Pedersen (page 14). In response this argument, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In the instant case, as discussed above, since Cocuzza taught that digoxigenin-mediated capture was an art-recognized equivalent of the biotin-avidin capture method taught by Pedersen (column 7, lines 28-43), an ordinary artisan would have been motivated to substitute one nucleic acid purification method for the other with a reasonable expectation of success. As noted in MPEP 2144.06, the substitution of art-recognized equivalents known to be useful for the same purpose is *prima facie* obvious in the absence of unexpected results. In this case, no evidence of unexpected results with respect to the use of digoxigenin has been presented, and therefore, the substitution of one art-recognized equivalent for another is *prima facie* obvious. Since Applicant's arguments were not persuasive, the rejection has been maintained.

Rejections under 35 U.S.C. 103(a) citing Kinzler as the primary reference

The rejection of claims 9, 10, 12, 14-16, and 58 under 35 U.S.C. 103(a) as being unpatentable over Kinzler in view of Carninci and the rejection of claims 13 and 57 under 35 U.S.C. 103(a) as being unpatentable over Kinzler in view of Carninci and further in view of Edery and further in view of Das have been withdrawn in view of the claim amendments. Specifically, the combined teachings of these references do not suggest ligating a linker to the end of a cDNA molecule that corresponds to the most 5' end of an mRNA molecule as required by step (b) in amended independent claims 9 and 12. Accordingly, Applicant's arguments filed on August 13, 2009 regarding these rejections have been considered, but they are moot in view of the new grounds of rejection presented above.

Conclusion

14. No claims are currently allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANGELA BERTAGNA whose telephone number is (571)272-8291. The examiner can normally be reached on M-F, 9- 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached at 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

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/Angela M Bertagna/
Examiner, Art Unit 1637